

RAPID DEUTERIUM AND TRITIUM LABELLING OF AROMATIC COMPOUNDS USING ALKYL-  
ALUMINIUM DIHALIDE CATALYSTS: COMPETING REARRANGEMENT OF POLYSUBSTITUTED  
AROMATICS

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(Received in UK 14 August 1973; accepted for publication 6 September 1973)

A wide range of metal halide catalysts have recently been found to catalyze deuterium and tritium labelling of aromatic compounds.<sup>1,2,3</sup> The most thoroughly investigated of these catalysts are the organoaluminium dihalides which, in the presence of traces of water as co-catalyst, induce rapid exchange of isotopic hydrogen between perdeuterobenzene and other aromatic compounds; equilibrium is often attained within minutes at room temperature.<sup>1</sup> This deuterium-labelling technique is of considerable value, not only because it is the fastest known one-step procedure for aromatic deuteration, but also because the labelled compound in most cases is recovered quantitatively.

A modification of the above method allows tritium labelling.<sup>2</sup> The organoaluminium dihalide is dissolved in the aromatic compound to be labelled (or alternatively both the compound and the catalyst are dissolved in an alkane solvent), and this solution is exposed to a small amount of tritiated water of high specific activity. Rapid hydrolysis of the catalyst occurs along with the simultaneous incorporation of tritium into the organic compound. An important advantage of this method of tritium labelling is that the labelled products may be obtained with high radiochemical as well as chemical purity. The trace amounts of high specific activity impurities commonly produced by other tritium labelling techniques are not encountered.<sup>4</sup>

We now report that during the labelling of some disubstituted benzenes accompanying rearrangement of aromatic substituents has been observed, and caution is necessary in the application of the labelling technique to such classes of compounds. Thus in the deuteration of the xylenes using

benzene- $d_6$  as source of isotope, two concurrent reactions, in addition to labelling of the xylene, are possible. The xylenes may isomerise, or intermolecular migration of  $CH_3$  to the benzene- $d_6$  to yield toluene may occur.

The table shows that deuteration of the xylenes is much faster than isomerisation or intermolecular migration of a methyl group (to give toluene). Negligible migration is observed at  $25^\circ$  whereas all three xylenes have deuterated almost to equilibrium after 15 minutes at this temperature. Similarly m-diethylbenzene can be deuterated at  $25^\circ$  with only slight migration of an ethyl group to benzene. Substantial substituent migration is observed with both xylenes and m-diethylbenzene at elevated temperatures. Thus the labelling technique does appear to be applicable to dialkylbenzenes, but care is necessary in the choice of reaction conditions.

In contrast, the dibromobenzenes and bromotoluene are likely to undergo extensive intermolecular transfer of the bromo group whenever deuteration is accomplished. The exact extent to which this rearrangement occurs appears to depend on the precise reaction conditions. This effect is under further study. However short reaction periods and low temperatures favour exchange with a minimum of rearrangement. Chloro substituents appear to be relatively non labile, while iodo substituents may be even more labile. Extensive migration of bromo groups was also observed in the more highly substituted tetrabromobenzene.

The nature of the co-catalyst in these reactions is also important. As an alternative to water,  $^1H$  hydrogen chloride is useful as a co-catalyst. If the addition of the hydrogen chloride ( $< 1 HCl$  per  $EtAlCl_2$ ) is carefully controlled, it is sometimes possible to achieve deuteration without extensive rearrangement of labile substituents. In this way we have deuterated o-dibromobenzene and p-chlorobromobenzene mainly to the  $d_4$  state, with less than 25% cleavage to monobromobenzene.

We thus wish to emphasise that care should be exercised in the labelling of polysubstituted aromatics by the present method. Most aromatic compounds are amenable to deuteration and tritiation, since a reaction temperature can be selected such that competing rearrangement reactions are much slower than isotope incorporation. However, with a few compounds, particularly the bromopolysubstituted aromatics, current evidence indicates that rearrangement reactions may predominate.

TABLE. Reactions of Polysubstituted Benzenes on Attempted Aromatic Deuteration with Benzene-d<sub>6</sub>.<sup>a</sup>

Disubstituted benzene	Conditions	Products	Extent of deuteration <sup>b</sup>
<u>o,m</u> or <u>p</u> -xylene	25°, 30 min.	unchanged <u>o,m</u> , or <u>p</u> -xylene	d <sub>4</sub>
<u>o</u> -xylene	110°, 15 h.	<u>o</u> -xylene, <u>m</u> -xylene, <u>p</u> -xylene and toluene (8:20:9:14)	d <sub>4</sub>
<u>m</u> -xylene	110°, 15 h.	<u>o</u> -xylene, <u>m</u> -xylene, <u>p</u> -xylene and toluene (8:20:9:8)	d <sub>4</sub>
<u>p</u> -xylene	110°, 15 h.	<u>o</u> -xylene, <u>m</u> -xylene, <u>p</u> -xylene and toluene (4:20:12:3)	d <sub>4</sub>
<u>m</u> -diethylbenzene	25°, 30 min.	<u>m</u> -diethylbenzene, ethylbenzene (15:1)	d <sub>4</sub> -d <sub>5</sub>
<u>m</u> -diethylbenzene	25°, 15 h.	<u>m</u> -diethylbenzene, ethylbenzene (5:2)	d <sub>4</sub> -d <sub>5</sub>
<u>m</u> -diethylbenzene	105°, 15 h.	<u>o,m,p</u> -diethylbenzene ethylbenzene (1:4)	d <sub>4</sub> -d <sub>5</sub>
<u>o</u> -dibromobenzene	25°, 3 min.	70% <u>o</u> -dibromobenzene 30% bromobenzene	d <sub>3</sub> -d <sub>4</sub> d <sub>4</sub> -d <sub>5</sub>
<u>o</u> -dibromobenzene	25°, 15 h.	30% <u>o</u> -dibromobenzene 70% bromobenzene	d <sub>3</sub> -d <sub>4</sub> d <sub>4</sub> -d <sub>5</sub>
<u>p</u> -dibromobenzene	25°, 15 h.	10% <u>p</u> -dibromobenzene 90% bromobenzene	d <sub>3</sub> -d <sub>4</sub> d <sub>4</sub> -d <sub>5</sub>
<u>p</u> -dibromobenzene	105°, 15 h.	100% bromobenzene	d <sub>4</sub> -d <sub>5</sub>
<u>p</u> -dichlorobenzene	25°, 30 min.	100% <u>p</u> -dichlorobenzene	d <sub>3</sub> -d <sub>4</sub>
<u>p</u> -dichlorobenzene	25°, 15 h.	100% <u>p</u> -dichlorobenzene	d <sub>3</sub> -d <sub>4</sub>
<u>p</u> -dichlorobenzene	105°, 15 h.	100% <u>p</u> -dichlorobenzene	d <sub>3</sub> -d <sub>4</sub>
<u>o</u> -bromotoluene	25°, 15 h.	ca. 80% toluene ca. 80% bromobenzene ca. 20% <u>o</u> -bromotoluene	d <sub>4</sub> -d <sub>5</sub> d <sub>4</sub> -d <sub>5</sub> d <sub>3</sub> -d <sub>4</sub>
<u>o,m</u> , or <u>p</u> -bromo-toluene	105°, 15 h.	90-95% toluene 90-95% bromobenzene 5-10% recovered bromotoluene	d <sub>4</sub> -d <sub>5</sub> d <sub>4</sub> -d <sub>5</sub> d <sub>3</sub> -d <sub>4</sub>
tetrabromobenzene	80°, 2 h.	100% bromobenzene	d <sub>4</sub> -d <sub>5</sub>

<sup>a</sup> Typical reaction procedure: 1  $\mu$ l water then 0.2 ml of 0.6M EtAlCl<sub>2</sub>/C<sub>6</sub>D<sub>6</sub> were added to 0.1 ml disubstituted benzene. At the end of reaction the sealed ampoule was opened, the EtAlCl<sub>2</sub> was destroyed by dil. aq. HCl, and the aromatic compounds were analyzed by glc and mass spectrometry.

<sup>b</sup> These data represent the largest peak in the low voltage mass spectrum. In all cases the deuterium distribution is close to that expected at equilibrium

Acknowledgements

We thank the Australian Research Grants Committee and the Australian Institute of Nuclear Science & Engineering for their support of the research at the University of New South Wales.

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